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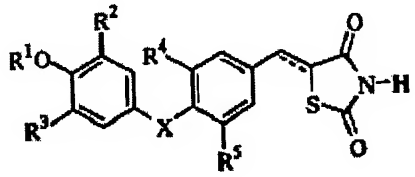
(54) [ Title of the Invention ]**Substance With Thyroid Hormone-Like Action**

(57) [ Abstract ]

[ Means ] Compounds represented by Formula (I) or salts thereof (where $R^1$ is a hydrogen atom or $C_1$ to $C_6$ alkyl; $R^2$, $R^3$, $R^4$, and $R^5$ are each independently a hydrogen atom, halogen atom, or $C_1$ to $C_6$ alkyl; X is -O-, -S-, -$NR^6$-, -$C(R^7)(R^8)$-, -$CH(OR^9)$-, or -CO- (where $R^6$, $R^7$, $R^8$, and $R^9$ are each independently a hydrogen atom or $C_1$ to $C_6$ alkyl), and = is a single or double bond).

[ Merit ] The invention has thyroid hormone-like action, making it useful as an active ingredient in medicinal compositions for the treatment and/or prevention of diseases such as obesity, hypercholesterolemia, and atherosclerosis.

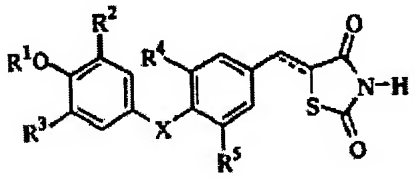
[ Chemical Formula 1 ]



[ Claims ]

[ Claim 1 ] A compound represented by the following General Formula (I) or salt thereof (where $R^1$ is a hydrogen atom or $C_1$ to $C_6$ alkyl; $R^2$, $R^3$, $R^4$, and $R^5$ are each independently a hydrogen atom, halogen atom, or $C_1$ to $C_6$ alkyl; X is -O-, -S-, -$NR^6$-, -$C(R^7)(R^8)$-, -$CH(OR^9)$-, or -CO- (where $R^6$, $R^7$, $R^8$, and $R^9$ are each independently a hydrogen atom or $C_1$ to $C_6$ alkyl), and = is a single or double bond).

[ Chemical Formula 1 ]



[ Claim 2 ] A compound or salt according to Claim 1, wherein X is -O-.

[ Claim 3 ] A medicinal composition, comprising as an active ingredient a compound or physiologically acceptable salt thereof according to Claim 1 or 2.

[ Claim 4 ] An agent with thyroid hormone-like action, comprising as an active ingredient a compound or physiologically acceptable salt thereof according to Claim 1 or 2.

[ Detailed Description of the Invention ]

[ 0001 ]

[ Technical Field to Which the Invention Belongs ]

The present invention relates to novel compounds having thyroid hormone-like action.

[ 0002 ]

[ Prior Art ]

The active principal of thyroid hormone is 3,5,3'-triiodothyronine, which plays a major role in regulating the metabolism, growth, and differentiation of vertebrates. Thyroid hormone manifests action by binding as a ligand to thyroid hormone receptor (TR) belonging to the nuclear receptor superfamily (Evans, R.M., *Science*, **240**, p. 889 (1988)) to activate or control transcription of the target gene. Thyroid hormone controls, for example, action on the cardiovascular system, energy metabolism, lipid metabolism, and the like, with the potential for serving as a drug in the clinical treatment of obesity, hypercholesterolemia, and atherosclerosis. However, because of adverse reactions such as angina pectoris and myocardial infarction due to various types of physiological action, there is a need to develop novel substances with thyroid hormone-like action.

[ 0003 ]

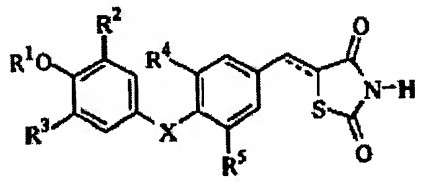
[ Problems Which the Invention Is Intended to Solve and Means for Solving the Abovementioned Problems ]

An object of the invention is to provide compounds exhibiting thyroid hormone-like action through action on thyroid hormone receptors. As a result of extensive research to overcome the above drawbacks, the inventors perfected the present invention upon finding that novel compounds represented by General Formula (I) below have thyroid hormone-like action.

[ 0004 ]

That is, the present invention is intended to provide a compound represented by the following General Formula (I) or salt thereof (where $R^1$ is a hydrogen atom or $C_1$ to $C_6$ alkyl; $R^2$, $R^3$, $R^4$, and $R^5$ are each independently a hydrogen atom, halogen atom, or $C_1$ to $C_6$ alkyl; X is -O-, -S-, $-NR^6-$, $-C(R^7)(R^8)-$, $-CH(OR^9)-$, or -CO- (where $R^6$, $R^7$, $R^8$, and $R^9$ are each independently a hydrogen atom or $C_1$ to $C_6$ alkyl), and = is a single or double bond).

[ Chemical Formula 2 ]



[ 0005 ]

In another aspect, the invention is intended to provide a medicinal composition comprising as an active ingredient a compound represented by the above General Formula (I) or a physiologically acceptable salt thereof. The medicinal composition would be useful for the treatment and/or prevention of diseases such as obesity, hypercholesterolemia, and atherosclerosis. The invention is also intended to provide an agent with thyroid hormone-like action comprising as an active ingredient a compound represented by the above General Formula (I) or a physiologically acceptable salt thereof. The invention is furthermore intended to provide a method for the use of a compound represented by the above General Formula (I) or a physiologically acceptable salt thereof to produce the above medicinal composition, and a method for the treatment and/or prevention of diseases such as obesity, hypercholesterolemia, and atherosclerosis, comprising the step of administering a compound represented by the above General Formula (I) or a physiologically acceptable salt thereof to mammals, including humans, in an amount that is effective for therapeutic and/or prophylactic purposes.

[ 0006 ]

[ Embodiments of the Invention ]

As used in the present Specification, $C_1$ to $C_6$ alkyls are straight chain, branched, cyclic, or a combination thereof. Examples include methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclopropylmethyl, n-pentyl, isopentyl, neopentyl, cyclobutylmethyl, n-hexyl, and cyclohexyl groups. As used in the present Specification, halogen atoms refer to any of fluorine, chlorine, bromine, or iodine atoms.

[ 0007 ]

X is preferably an oxygen atom. The halogen atoms represented by $R^2$, $R^4$, and $R^5$ are preferably iodine atoms. The halogen atom represented by $R^3$ is preferably a bromine or iodine atom. The alkyls represented by $R^2$ and $R^3$ are preferably bulky alkyls such as isopropyl, isobutyl, and tert-butyl groups. Alkyls represented by $R^1$, $R^4$, and $R^5$ are preferably methyl.

[ 0008 ]

The compounds of the present invention sometimes occur in the form of salts. They also sometimes have one or more asymmetrical carbons depending on the type of substituent, but the

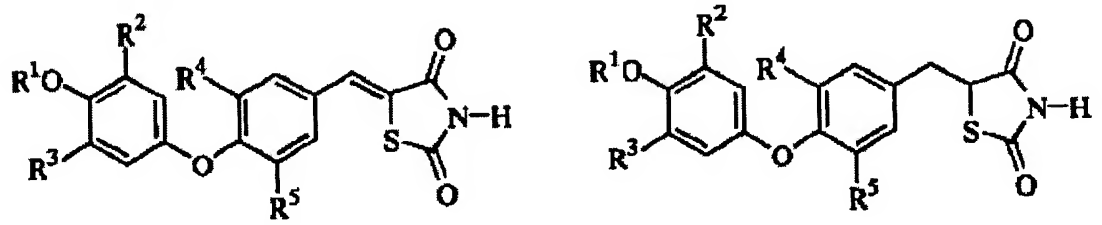
configuration of the asymmetrical carbons is not particularly limited. The invention encompasses any salt, asymmetrical carbon-based optical active form, stereoisomer such as diastereoisomers, any mixture of stereoisomers, racemates, or the like. The invention also encompasses hydrates and solvates of the above compounds or salts.

[ 0009 ]

Preferred compounds of the invention represented by General Formula (I) include compounds in which X is -O-, but the invention is not limited to such compounds.

[ 0010 ]

[ Chemical Formula 3 ]



[ 0011 ]

[ Table 1 ]

| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|
| 1 | H | H | I | I | I |
| 2 | H | I | I | I | I |
| 3 | $CH_3$ | I | I | I | I |
| 4 | H | H | Br | I | I |
| 5 | H | H | *tert*Bu | I | I |
| 6 | $CH_3$ | H | *tert*Bu | I | I |
| 7 | $CH_3$ | *tert*Bu | *tert*Bu | I | I |
| 8 | H | H | isoPr | I | I |
| 9 | H | H | isoPr | H | H |
| 10 | H | H | isoPr | $CH_3$ | $CH_3$ |
| 11 | H | H | I | I | I |
| 12 | H | H | *tert*Bu | I | I |
| 13 | H | H | isoPr | I | I |
| 14 | H | H | isoPr | H | H |
| 15 | H | H | isoPr | $CH_3$ | $CH_3$ |

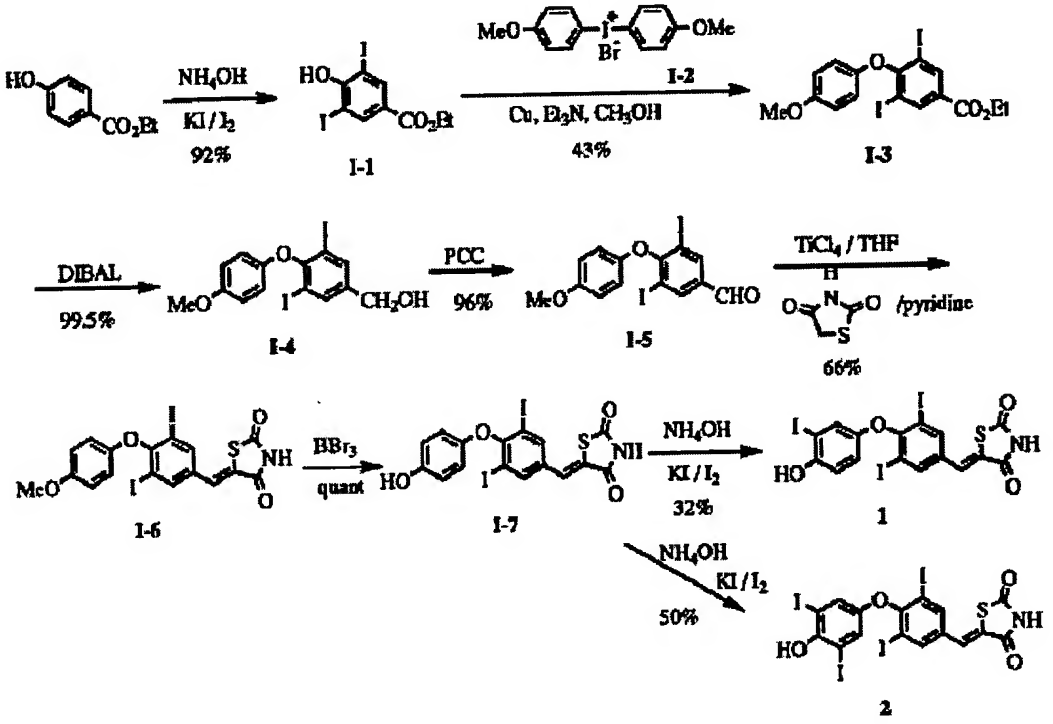
[ 0012 ]

Typical examples of compounds of the invention are given in the following schemes of methods for producing Compounds 1 through 15 of the following chemical formulas. Specific methods for producing these compounds are illustrated in detail in the examples. The methods for producing the compounds of the invention are not limited, of course, to those given in the following schemes. Those having ordinary skill in the art will be able to produce any of the

compounds of the invention included in General Formula (I) by selecting starting material compounds, reaction conditions, reagents, and the like with reference to the following methods and examples, and by modifying or improving such methods as needed.

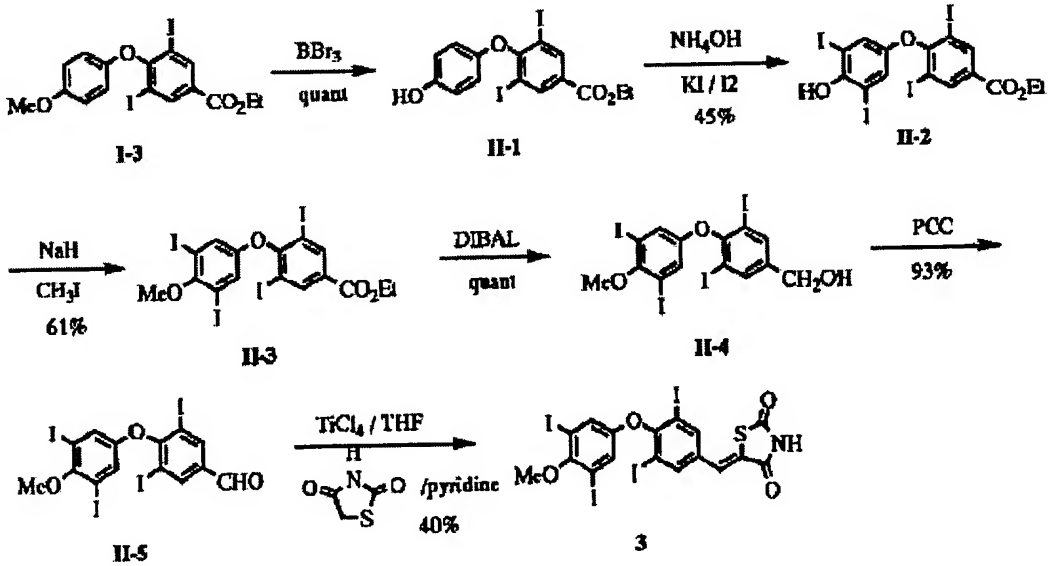
[ 0013 ]

[ Chemical Formula 4 ]



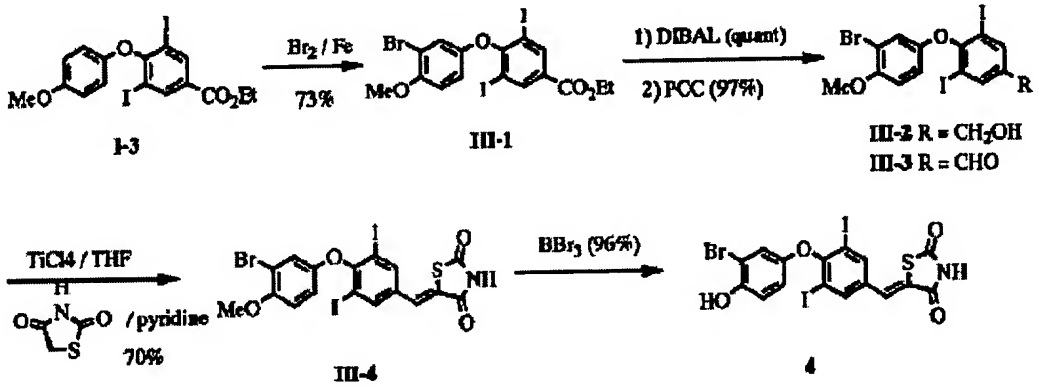

[ 0014 ]

[ Chemical Formula 5 ]



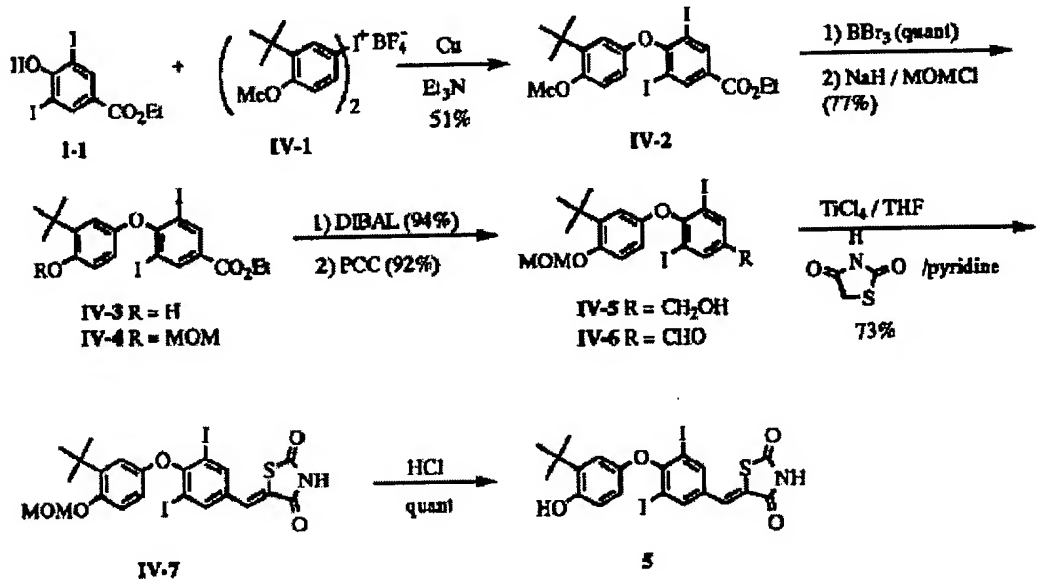
[ 0015 ]

[ Chemical Formula 6 ]



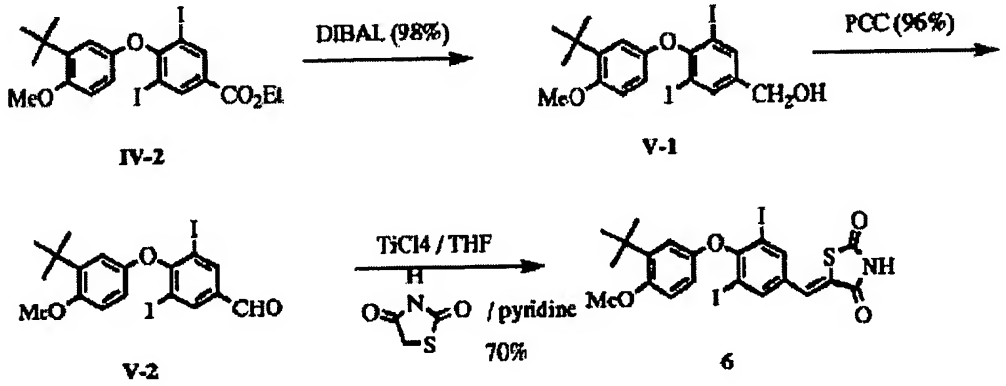

[ 0016 ]

[ Chemical Formula 7 ]



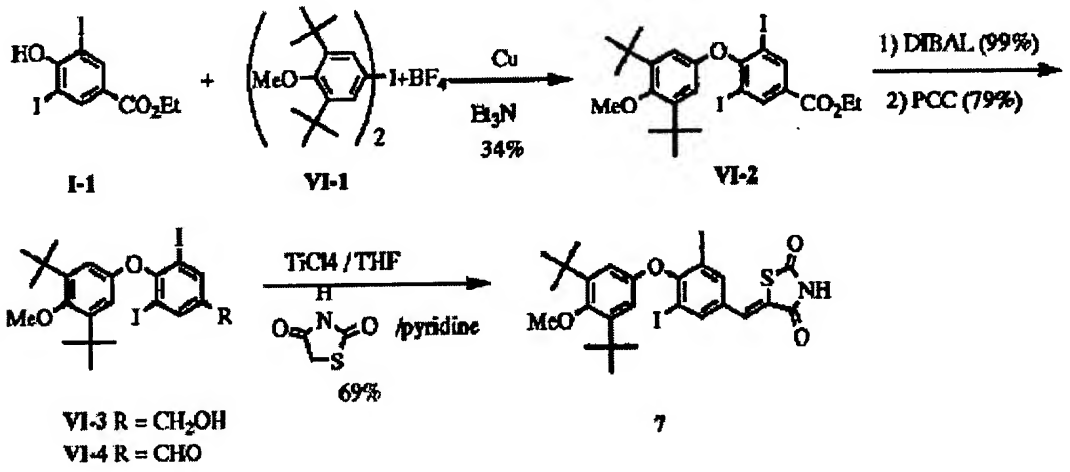

[ 0017 ]

[ Chemical Formula 8 ]



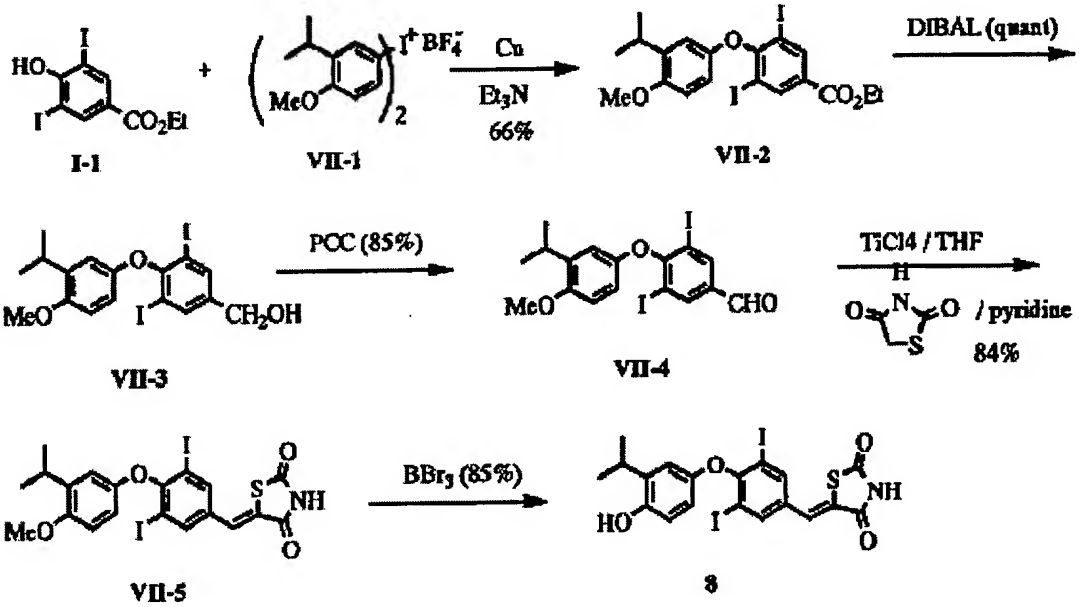
[ 0018 ]

[ Chemical Formula 9 ]



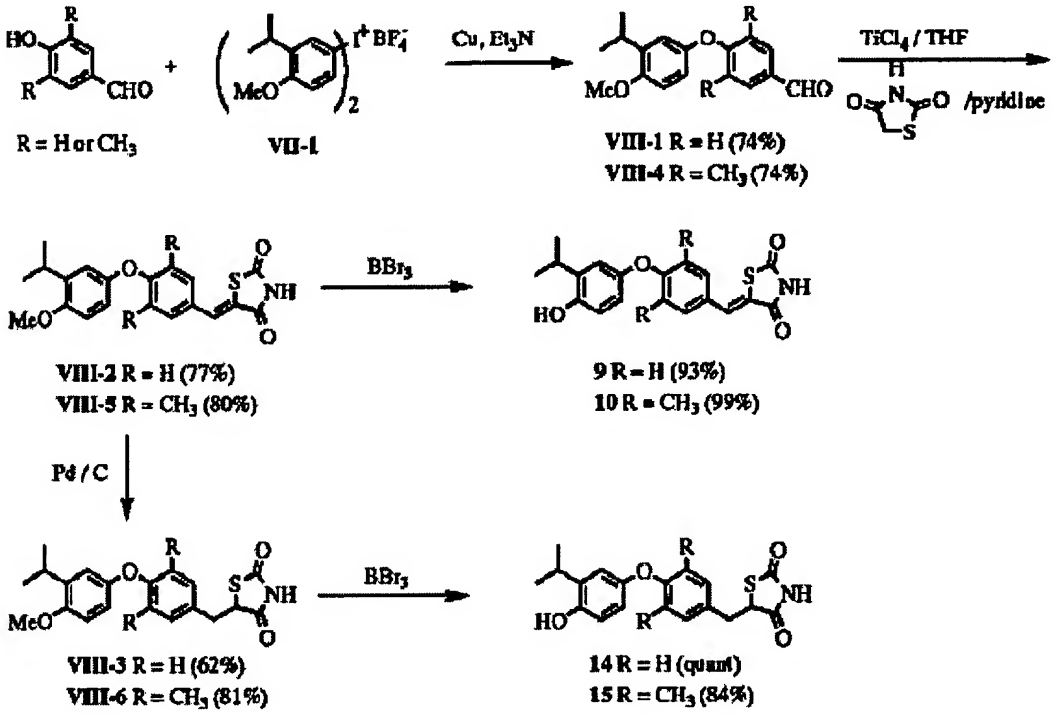

[ 0019 ]

[ Chemical Formula 10 ]



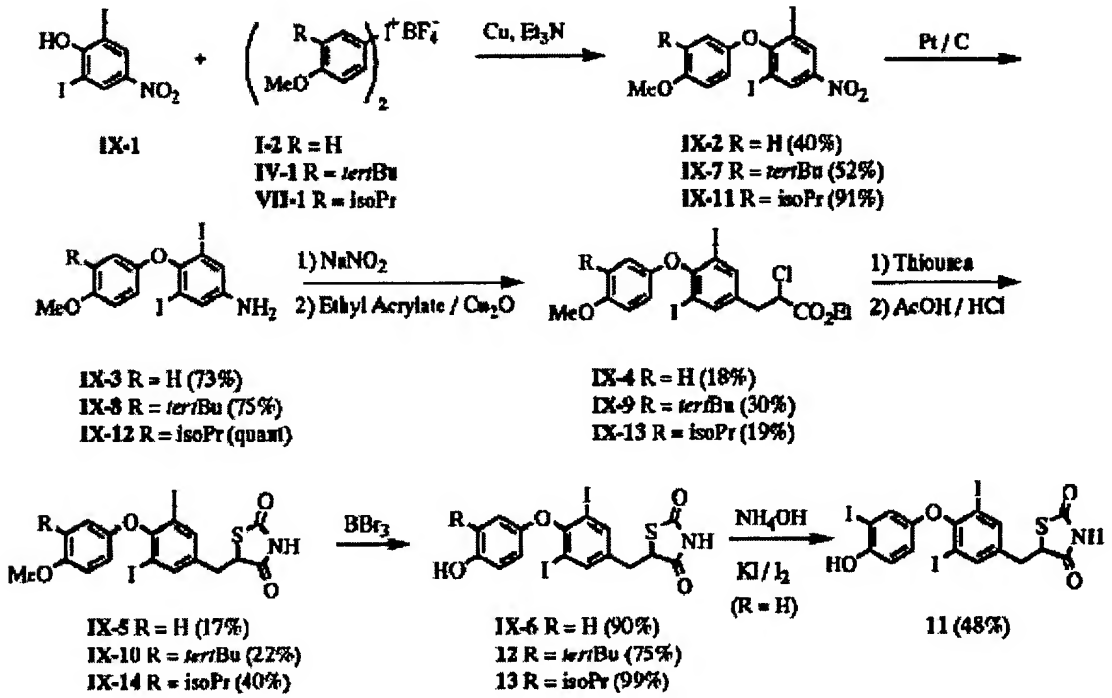
[ 0020 ]

[ Chemical Formula 11 ]




[ 0021 ]

[ Chemical Formula 12 ]



[ 0022 ]

The compounds of Formula (I) bind to nuclear thyroid hormone receptors to activate the receptors and manifest thyroid hormone-like action. The compounds of the invention may therefore be useful in the treatment and/or prevention of diseases such as obesity, hypercholesterolemia, and atherosclerosis. Compounds of General Formula (I) or their salts, hydrates, and solvates can be used as active ingredients in the medicinal compositions of the present invention. The above active ingredients may be given as such in the form of the medicinal compositions of the present invention, but they should generally be prepared in the form of medicinal compositions which include one or more pharmaceutical additives in addition to the above active ingredients. The route of administration by which the medicinal composition is given in the present invention is not limited, and includes oral and parenteral administration.

[ 0023 ]

Examples of medicinal compositions suitable for oral administration include tablets, capsules, dispersions, subtilized granules, granules, liquids, and syrups. Examples of medicinal compositions suitable for parenteral administration include injections, drip infusion agents, suppositories, inhalants, ophthalmic solutions, nasal drops, transdermal absorption agents, ointments, creams, and patches. Examples of pharmaceutical additives include excipients, disintegrants or disintegrant aids, binders, lubricants, coating agents, colorants, diluents, bases, dissolving agents or dissolving aids, isotonic agents, pH regulators, stabilizers, propellants, and adhesives, which should be selected according to the type of medicinal composition. The dose is not particularly limited, and can be selected depending on conditions such as the type of compound serving as the active ingredient, the purpose of the prophylaxis or therapy, the type of disease being treated, the patient's age and condition, and the route of administration.

[ 0024 ]

[ Examples ]

The invention is illustrated in further detail in the following examples, but the scope of the invention is not limited by the following examples. Compound numbers and manufacturing steps in the examples are the same as in the above schemes.

Example 1 : Synthesis of Compound 1

10.00 g (60.24 mmol) ethyl 4-hydroxybenzoate was dissolved in 180 mL aqueous ammonia. 124 g (747 mmol) potassium iodide and 36.7 g (145 mmol) iodine were dissolved in 120 mL water and stirred into the above solution. After 24 hours, concentrated hydrochloric acid was added to render the solution acidic, and the solution was extracted with ether. The organic phase was washed with water and aqueous sodium chloride, and was then dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (methylene chloride:n-hexane = 1:1), giving 23.26 g (92%) Compound I-1.

Compound I-1: $^1$H-NMR (400 MHz, $CDCl_3$) 8.36 (s, 2 H), 6.12 (s, 1 H), 4.35 (q, J = 8.1 Hz, 2 H), 1.39 (t, J = 7.2 Hz, 3 H).

[ 0025 ]

1 mL triethylamine, 0.7 g copper powder, and 20 mL anhydrous methanol were added to 2.00 g (4.78 mmol) Compound I-1 and 4.03 g (9.57 mmol) Compound I-2, and the ingredients were stirred for 24 hours at room temperature. The copper was filtered off, and the filtrate was concentrated and then extracted with ethyl acetate. The organic phase was washed with 1 N hydrochloric acid, water, 1 N sodium hydroxide aqueous solution, water, and aqueous sodium chloride, and it was then dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:6), giving 1.14 g (43%) of a 4:1 mixture of Compound I-3 and p-dimethoxybenzene.

Compound I-3:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.51 (s, 2 H), 6.83 (d, J = 6.4 Hz, 2 H), 6.70 (d, J = 6.8 Hz, 2 H), 4.39 (q, J = 7.1 Hz, 2 H), 3.78 (s, 3 H), 1.40 (t, J = 7.2 Hz, 3 H).

[ 0026 ]

1.13 g (2.16 mmol) Compound I-3 was dissolved in 6 mL of tetrahydrofuran (THF), and 6.47 mL (6.47 mmol) DIBAL (1 M toluene solution) was gradually stirred in at 0°C. After 20

minutes, the reaction solution was poured into 2 N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:2), giving 951 mg (99.5%) Compound I-4.

Compound I-4:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.86 (s, 2 H), 6.82 (d, J = 8.2 Hz, 2 H), 6.71 (d, J = 9.3 Hz, 2 H), 4.66 (s, 2 H), 3.77 (s, 3 H), 1.83 (br s, 1 H).

[ 0027 ]

880 mg (1.83 mmol) Compound I-4 was dissolved in 8 mL of methanol-free methylene chloride, and 1.18 g (5.48 mmol) PCC was stirred in at room temperature. After 1 hour, the solution was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:4), giving 838 mg (96%) Compound I-5.

Compound I-5:

$^1$H-NMR (400 MHz, $CDCl_3$) 9.87 (s, 1 H), 8.35 (s, 2 H), 6.84 (d, J = 9.2 Hz, 2 H), 6.71 (d, J = 9.2 Hz, 2 H), 3.78 (s, 3 H)

[ 0028 ]

596 mg (1.72 mmol) $TiCl_4$ was dissolved in 1 mL of carbon tetrachloride, and the solution was gradually added over a period of 15 minutes to 3 mL THF cooled on ice in an argon atmosphere. When a yellow precipitate was produced, a 3 mL THF solution of 200 mg (0.42 mmol) Compound I-5, 58.5 mg (0.5 mmol) thiazolidinedione, and 1 mL (12.4 mmol) anhydrous pyridine was added at 0°C, and the mixture was stirred for 23 hours at room temperature. Ethyl acetate was added to the reaction solution, and the solids were filtered off. The filtrate was washed with water, 2 N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and aqueous sodium chloride, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:2 → 1:1), giving 158 mg (66%) Compound I-6.

Compound I-6

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.14 (br s, 1 H), 8.12 (s, 2 H), 7.75 (s, 1 H), 6.89 (d, J = 9.3 Hz, 2 H), 6.69 (d, J = 9.0 Hz, 2 H), 3.72 (s,3 H)

[ 0029 ]

140 mg (0.24 mmol) Compound I-6 was suspended in 4 mL of methanol-free methylene chloride, 0.97 mL (0.97 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the mixture was stirred for 2 hours at 0°C. Water was added to the reaction solution, and it was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate aqueous solution and aqueous sodium chloride, and it was dried over $MgSO_4$. The solvent was distilled off, giving 136 mg (quantitative) crude product of Compound I-7.

Compound I-7

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.70 (br s, 1 H), 9.11 (s, 1 H), 8.10 (s, 2 H), 7.63 (s, 1 H), 6.70 (d, J = 9.0 Hz, 2 H), 6.57 (d, J = 9.0 Hz,2 H)

[ 0030 ]

140 mg (0.25 mmol) Compound I-7 was dissolved in 10 mL aqueous ammonia. 255 mg (1.54 mmol) potassium iodide and 75.5 mg (0.30 mmol) iodine were dissolved in 5 mL water and added to the above, and the mixture was stirred at room temperature. After 7 hours, the solution was rendered acidic with 2 N hydrochloric acid, and it was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1), giving 55 mg (32%) Compound 1.

Compound 1: yellow needle-shaped crystals (ethyl acetate/n-hexane); m.p. 261°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.76 (br s, 1 H), 10.00 (s, 1 H), 8.11(s, 1 H), 7.75 (s, 1 H), 7.08 (d, J = 2.9 Hz, 1 H), 6.82 (d, J = 8.8 Hz,1 H), 6.60 (dd, J = 8.8, 2.9 Hz, 1 H);
Anal. calcd for $C_{16}H_8NO_4SI_2$ C: 27.81 %, H: 1.17 %, N: 2.03 %, Found C:27.95 %, H: 1.40 %, N: 2.20 %

[ 0031 ] Example 2: Synthesis of Compound 2

300 mg (0.53 mmol) Compound I-7 was dissolved in 10 mL aqueous ammonia. 1.09 g (6.58 mmol) potassium iodide and 297 mg (1.17 mmol) iodine were dissolved in 8 mL water and stirred into the above solution at room temperature. After 2.5 hours, 2 N hydrochloric acid was added to the reaction solution to render it acidic, and it was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 3:2), giving 185 mg (50%) Compound 2.

Compound 2: yellowish powder (DMF/ethyl acetate/n-hexane); m.p. > 300°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.72 (br s, 1 H), 9.56 (s, 1 H), 8.12 (s, 2 H), 7.75 (s, 1 H), 7.14 (s, 2 H);
Anal. Calcd for $C_{16}H_7NO_4SI_4$ C: 23.52 %, H: 0.86 %, N: 1.71 %, Found C:23.46 %, H: 1.11 %, N: 1.77 %

[ 0032 ] Example 3: Synthesis of Compound 3

989 mg (1.89 mmol) Compound I-3 was dissolved in 10 mL anhydrous methylene chloride, 5.7 mL (5.7 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the mixture was stirred for 2 hours. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and extracted with methylene chloride. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 3:8), giving 1.02 g (quantitative) Compound II-1.

Compound II-1:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.51 (s, 2 H), 6.77 (d, J = 8.7 Hz, 2 H), 6.66 (d, J = 8.9 Hz, 2 H), 4.59 (s, 1 H), 4.39 (q, J = 6.7 Hz, 2 H), 1.41 (t, J = 7.0 Hz, 3 H)

[ 0033 ]

393 mg (0.77 mmol) Compound II-1 was dissolved in 10 mL methanol. 10 mL aqueous ammonia along with 793 mg (4.78 mmol) potassium iodide and 234 mg (0.92 mmol) iodine

dissolved in 5 mL water were added, and the ingredients were stirred for 40 minutes at room temperature. Concentrated hydrochloric acid was added while cooled on ice to render the solution acidic, and it was extracted with ethyl acetate. The organic phase was washed with sodium bisulfite aqueous solution and aqueous sodium chloride, and it was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (methylene chloride:n-hexane = 1:1), giving 263 mg (45%) Compound II-2.

Compound II-2:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.51 (s, 2 H), 7.11 (s, 2 H), 5.50 (s, 1 H), 4.40 (q, J = 7.1 Hz, 2 H), 1.42 (t, J = 7.1 Hz, 3 H)

[ 0034 ]

21 mg (0.51 mmol) NaH (60% in oil) was washed with n-hexane, dried, and suspended in 1 mL DMF. 260 mg (0.34 mmol) Compound II-2 was dissolved in 3 mL DMF, and the ingredients were stirred with the above for 15 minutes at room temperature. 0.04 mL (0.68 mmol) $CH_3I$ was added to the reaction solution, and the mixture was stirred for 30 minutes. Water was added to the reaction solution, and it was extracted with ether. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, giving 162 mg (61%) crude product of Compound II-3.

Compound II-3:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.51 (s, 2 H), 7.16 (s, 2 H), 4.41 (q, J = 7.2 Hz, 2 H), 3.84 (s, 3 H), 1.42 (t, J = 7.1 Hz, 3 H)

[ 0035 ]

160 mg (0.21 mmol) Compound II-3 was dissolved in 5 mL of THF, 0.62 mL (0.62 mmol) DIBAL (1 M toluene solution) was gradually added at 0°C, and the ingredients were stirred. After 30 minutes, 2 N hydrochloric acid was poured in, and the mixture was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, giving 173 mg (quantitative) crude product of Compound II-4.

Compound II-4:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.87 (s, 2 H), 7.17 (s, 2 H), 4.69 (s, 2 H), 3.84 (s, 3 H)

[0036]

150 mg (20.4 mmol) Compound II-4 was dissolved in 2 mL of methanol-free methylene chloride, and 132 mg (0.61 mmol) of PCC was stirred in at room temperature. After 2 hours, the solution was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:4), giving 139 mg (93%) Compound II-5.

Compound II-5:

$^1$H-NMR (400 MHz, $CDCl_3$) 9.90 (s, 1 H), 8.36 (s, 2 H), 7.17 (s, 2 H), 3.85 (s, 3 H)

[0037]

107 mg (0.56 mmol) $TiCl_4$ dissolved in 0.8 mL of carbon tetrachloride was gradually added to 2 mL of THF while cooled on ice in an argon atmosphere. When yellow precipitate was produced, a 4 mL THF solution of 137 mg (0.19 mmol) Compound II-5, 26 mg (0.22 mmol) thiazolidinedione, and 0.2 mL (2.5 mmol) anhydrous pyridine was added at 0°C, and the ingredients were stirred for 20 hours at room temperature. The reaction solution was extracted with ethyl acetate, the solids were filtered off, and the filtrate was washed with water, 2 N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and aqueous sodium chloride, in that order, and it was dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:4 → 1:2), giving 63 mg (40%, starting material recovered 35 mg) of Compound 3.

Compound 3: colorless powder (DMF/ethyl acetate/n-hexane): m.p. > 300°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.73 (b, 1 H), 8.13 (s, 2 H), 7.74 (s,1 H), 7.23 (s, 2 H), 3.73 (s, 3 H);

Anal. Calcd for $C_{17}H_{15}NO_4SI_4$ C: 24.57 %, H: 1.69 %, N: 1.09 %, Found C:24.60 %, H: 1.49 %, N: 1.39 %

[ 0038 ] Example 4: Synthesis of Compound 4

431 mg (0.82 mmol) Compound I-3 (Scheme I) was dissolved in 8 mL carbon tetrachloride, and 55 mg (0.99 mmol) iron powder was added. 0.055 mL (1.07 mmol) bromine was added at room temperature, and the ingredients were stored for 1 hour at 60°C. The reaction solution was poured into sodium bisulfite aqueous solution, and it was extracted with methylene chloride. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:10), giving 362 mg (73%) Compound III-1.

Compound III-1:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.51 (s, 2 H), 7.03 (d, J = 2.9 Hz, 1 H), 6.82 (d, J = 9.0 Hz, 1 H), 6.65 (d d, J = 9.0, 3.0 Hz, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 3.86 (s, 3 H), 1.39 (t, J = 7.1 Hz, 3 H)

[ 0039 ]

355 mg (0.59 mmol) Compound III-1 was dissolved in 5 mL THF, and 1.77 mL (1.77 mmol) DIBAL (1 M toluene solution) was gradually added at 0°C and stirred for 30 minutes. The reaction solution was poured into 2 N hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, giving 360 mg (quantitative) Compound III-2.

Compound III-2:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.86 (s, 2 H), 7.02 (d, J = 2.9 Hz, 1 H), 6.82 (d, J = 9.1 Hz, 1 H), 6.69 (d d, J = 9.0, 3.0 Hz, 1 H), 4.68 (s, 2 H), 3.86 (s, 3 H)

[ 0040 ]

320 mg (0.57 mmol) Compound III-2 was dissolved in 6 mL of methanol-free methylene chloride, 246 mg (1.14 mmol) PCC was added, and the ingredients were stirred for 1 hour at room temperature. The reaction solution was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:4), giving 308 mg (97%) Compound III-3.

Compound III-3:

$^1$H-NMR (400 MHz, $CDCl_3$) 9.89 (s, 1 H), 8.35 (s, 2 H), 7.05 (d, J = 2.9 Hz, 1 H), 6.82 (d, J = 9.1 Hz, 1 H), 6.66 (dd, J = 9.0, 3.1 Hz, 1 H), 3.87 (s, 3 H)

[ 0041 ]

308 mg (1.61 mmol) $TiCl_4$ dissolved in 2 mL carbon tetrachloride was gradually added over a period of 15 minutes to 5 mL of THF while cooled on ice in an argon atmosphere. When yellow precipitate was produced, a 7 mL THF solution of 300 mg (0.54 mmol) Compound III-3, 75.3 mg (0.64 mmol) thiazolidinedione, and 0.56 mL (7.1 mmol) anhydrous pyridine was added at 0°C, and the mixture was stirred for 20 hours at room temperature. The reaction solution was extracted with ethyl acetate, the solids were filtered off, and the filtrate was washed with water, 2N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and aqueous sodium chloride, in that order, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1), giving 246 mg (70%) Compound III-4.

Compound III-4:

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.71 (b, 1 H), 8.12 (s, 2 H), 7.75 (s,1 H), 7.07 (d, J = 2.9 Hz, 1 H), 7.06 (d, J = 9.2 Hz, 1 H), 6.70 (dd, J= 9.1, 2.9 Hz, 1 H), 3.80 (s, 3 H)

[ 0042 ]

187 mg (0.28 mmol) Compound III-3 was suspended in 2 mL anhydrous methylene chloride, 0.85 mL (0.85 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 3 hours. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:methylene chloride = 1:2), giving 176 mg (96%) Compound 4.

Compound 4: colorless needle-shaped crystals (ethyl acetate/n-hexane); m.p. 253°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.68 (br, 1 H), 9.90 (s, 1 H), 8.11 (s,2 H), 7.73 (s, 1 H), 6.90 (d, J = 2.7 Hz, 1 H), 6.89 (d, J = 9.5 Hz, 1H), 6.59 (dd, J = 9.0, 2.7 Hz, 1 H);
Anal. Calcd for $C_{16}H_8NO_4SBrI_2$ C: 29.84 %, H: 1.25 %, N: 2.17 %, Found C: 29.64 %, H: 1.42 %, N: 1.92 %

[ 0043 ] Example 5: Synthesis of Compound 5

1 mL triethylamine, 0.70 g copper powder, and 20 mL anhydrous methylene chloride were added to 1.00 g (2.39 mmol) Compound I-1 and 1.55 g (2.87 mmol) Compound IV-1, and the mixture was stirred for 18 hours at room temperature. The copper was filtered off, the filtrate was concentrated, and it was then extracted with ethyl acetate. The organic phase was washed with 1 N hydrochloric acid, water, 1 N sodium hydroxide aqueous solution, water, and aqueous sodium chloride, in that order, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (methylene chloride:n-hexane = 1:8), giving 706 mg (51%) Compound IV-2.

Compound IV-2:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.04 (dd, J = 8.8, 2.4 Hz, 1 H), 7.96 (d, J = 2.4 Hz, 1 H), 7.10 (d, J = 9.0 Hz, 1 H), 3.85 (s, 3 H), 1.31 (s, 9 H)

[ 0044 ]

700 mg (1.21 mmol) Compound IV-2 was dissolved in 10 mL of anhydrous methylene chloride, 3.6 mL (3.6 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 2 hours at 0°C. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and was extracted with methylene chloride. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, giving 693 mg (quantitative) Compound IV-3.

Compound IV-3:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.50 (s, 2 H), 6.87 (d, J = 3.1 Hz, 1 H), 6.54 (d, J = 8.6 Hz, 1 H), 6.31 (d d, J = 8.6, 3.1 Hz, 1 H), 4.53 (br s, 1 H),4.39 (q, J = 7.2 Hz, 2 H), 1.41 (t, J = 7.2 Hz, 3 H), 1.38 (s, 9 H)

[ 0045 ]

72.9 mg (1.82 mmol) NaH (60% in oil) was washed with n-hexane and suspended in 1 mL DMF, 685 mg (1.21 mmol) Compound IV-3 was dissolved in 3 mL DMF and added, and the ingredients were stirred at room temperature. After 20 minutes, 0.18 mL (2.43 mmol) chloromethyl methyl ether was added, and the mixture was stirred at room temperature. After 30 minutes, water was added, and the material was extracted with ether. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:9), giving 397 mg Compound IV-4 and 173 mg of its MOM ester.

Compound IV-4:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.50 (s, 2 H), 6.97 (d, J = 9.0 Hz, 1 H), 6.89 (d, J = 3.1 Hz, 1 H), 6.37 (d d, J = 8.8, 3.1 Hz, 1 H), 5.17 (s, 2 H), 4.39 (q, J = 7.1 Hz, 2 H), 3.49 (s, 3 H), 1.41 (t, J = 7.1 Hz, 3 H), 1.36 (s, 9 H)

[ 0046 ]

395 mg (0.65 mmol) Compound IV-4 was dissolved in 3 mL THF, 1.95 mL (1.95 mmol) DIBAL (1 M toluene solution) was gradually added at 0°C, and the ingredient were stirred. After 20 minutes, the mixture was poured into water and extracted with ether. The organic phase was washed with 2 N hydrochloric acid and aqueous sodium chloride, and it was dried over $MgSO_4$. The solvent was distilled off, giving 347 mg (94%) crude product of Compound IV-5.

Compound IV-5:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.85 (s, 2 H), 6.96 (d, J = 9.0 Hz, 1 H), 6.91 (d, J = 3.1 Hz, 1 H), 6.36 (dd, J = 8.8, 3.1 Hz, 1 H), 5.16 (s, 2 H), 4.66 (s, 2 H), 3.49 (s, 3 H), 1.37 (s, 9 H)

[ 0047 ]

488 mg (0.86 mmol) Compound IV-5 was dissolved in 6 mL methanol-free methylene chloride, 557 mg (2.59 mmol) PCC was added, and the ingredients were stirred for 20 minutes at room temperature. Reaction solution was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:4), giving 445 mg (92%) Compound IV-6.

Compound IV-6:

$^1$H-NMR (400 MHz, $CDCl_3$) 9.88 (s, 1 H), 8.35 (s, 2 H), 6.99 (d, J = 9.1 Hz, 1 H), 6.90 (d, J = 3.1 Hz, 1 H), 6.38 (dd, J = 9.1, 3.1 Hz, 1 H), 5.18 (s, 2 H), 3.80 (s, 3 H), 1.37 (s, 9 H)

[ 0048 ]

445 mg (2.34 mmol) $TiCl_4$ dissolved in 2 mL carbon tetrachloride was added over a period of 15 minutes to 6 mL THF cooled on ice in an argon atmosphere. When yellow precipitate was produced, 5 mL of a THF solution of 440 mg (0.78 mmol) Compound IV-6, 110 mg (0.94 mmol) thiazolidinedione, and 0.8 mL (10.5 mmol) anhydrous pyridine was added at 0°C, and the mixture was stirred for 3.5 hours at room temperature. The reaction solution was extracted with ethyl acetate, the solids were filtered off, and the filtrate was washed with water, 2 N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and aqueous sodium chloride, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1), giving 377 mg (73%) Compound IV-7.

Compound IV-7:

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.70 (b, 1 H), 8.12 (s, 2 H), 7.75 (s,1 H), 6.96 (d, J = 9.0 Hz, 1 H), 6.81 (d, J = 3.2 Hz, 1 H), 6.39 (dd, J= 9.0, 3.1 Hz, 1 H), 5.19 (s, 2 H), 3.41 (s, 3 H), 1.34 (s, 9 H)

[ 0049 ]

97 mg (0.15 mmol) Compound IV-7 was dissolved in 4 mL THF, 1 mL concentrated hydrochloric acid was added, and the ingredients were stirred for 2 hours at 40°C. Water and ethyl acetate were added to the reaction solution. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 2:1), giving 95 mg (quantitative) Compound 5.

Compound 5: yellow needle-shaped crystals (ethyl acetate/n-hexane); m.p. 283°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.70 (b, 1 H), 9.08 (s, 1 H), 8.11 (s,2 H), 7.74 (s, 1 H), 6.71 (d, J = 3.0 Hz, 1 H), 6.66 (d, J = 8.5 Hz, 1 H), 6.25 (dd, J = 8.5, 2.9 Hz, 1 H), 1.31 (s, 9 H) ;
Anal. Calcd for $C_{20}H_{17}NO_4SI_2$ C: 38.67 %, H: 2.76 %, N: 2.25 %, Found C:38.39 %, H: 2.92 %, N: 2.23 %

[ 0050 ] Example 6: Synthesis of Compound 6

175 mg (0.30 mL) Compound IV-2 was dissolved in 4 mL THF, 0.91 mL (0.91 mmol) DIBAL was gradually added at 0°C, and the ingredients were stirred for 25 minutes. The reaction solution was poured into 2 N hydrochloric acid and extracted with ether. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, giving 158 mg (98%) crude product of Compound V-1.

Compound V-1:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.85 (s, 2 H), 6.92 (d, J = 3.2 Hz, 1 H), 6.70 (d, J = 8.8 Hz, 1 H), 6.38 (dd, J = 8.8, 3.1 Hz, 1 H), 4.66 (s, 2 H), 3.79 (s, 3 H), 1.55 (br s, 1 H), 1.35 (s, 9 H)

[ 0051 ]

155 mg (0.29 mmol) Compound V-1 was dissolved in 6 mL of methanol-free methylene chloride, 463 mg (2.15 mmol) PCC was added, and the ingredients were stirred for 20 minutes at room temperature. The reaction solution was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:4), giving 148 mg (96%) Compound V-2.

Compound V-2:

$^1$H-NMR (400 MHz, $CDCl_3$) 9.87 (s, 1 H), 8.34 (s, 2 H), 6.91 (d, J = 3.2 Hz, 1 H), 6.72 (d, J = 8.8 Hz, 1 H), 6.39 (dd, J = 8.8, 3.1 Hz, 1 H), 3.80 (s, 3 H), 1.35 (s, 9 H)

[ 0052 ]

152 mg (0.80 mmol) $TiCl_4$ dissolved in 1 mL carbon tetrachloride was added over a period of 15 minutes to 3 mL of THF cooled on ice in an argon atmosphere. When yellow precipitate was produced, a 4 mL THF solution of 143 mg (0.27 mmol) Compound V-2, 37 mg (0.32 mmol) thiazolidinedione, and 0.3 mL (3.6 mmol) anhydrous pyridine was added at 0°C, and the ingredients were stirred for 4 hours at room temperature. The reaction solution was extracted with ethyl acetate, the solids were filtered off, and the filtrate was washed with water, 2 N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and aqueous sodium chloride, in that order, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1), giving 96 mg (58%) Compound 6.

Compound 6: yellow needle-shaped crystals (ethyl acetate); m.p. 282°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.71 (b, 1 H), 8.122 (s, 1 H), 8.121 (s, 1 H), 7.75 (s, 1 H), 6.88 (d, J = 9.0 Hz, 1 H), 6.80 (d, J = 3.2 Hz, 1H), 6.38 (dd, J = 8.8, 3.0 Hz, 1 H), 3.76 (s, 3 H), 1.31 (s, 9 H)

[ 0053 ] Example 7: Synthesis of Compound 7

20 mL anhydrous methylene chloride was added to 2.00 g (4.78 mmol) Compound I-1, 3.74 g (5.74 mmol) Compound VI-1, 0.70 g copper powder, and 1 mL triethylamine, and the

ingredients were stirred for 6.5 hours at room temperature. The copper was filtered off, and the filtrate was concentrated and then extracted with methylene chloride. The organic phase was washed with 1 N hydrochloric acid and aqueous sodium chloride, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:12), giving 1.03 g (34%) Compound VI-2.

Compound VI-2:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.51 (s, 2 H), 6.65 (s, 2 H), 4.39 (q, J = 7.2 Hz, 2 H), 3.67 (s, 3 H), 1.40 (t, J = 6.7 Hz, 2 H), 1.36 (s, 18 H)

[ 0054 ]

1.03 g (1.62 mmol) Compound VI-2 was dissolved in 10 mL THF, 4.86 mL (4.86 mmol) DIBAL (1 M toluene solution) was gradually added at 0°C, and the ingredients were stirred for 30 minutes. The reaction solution was added to 2 N hydrochloric acid and extracted with ether. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. It was concentrated and then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:4), giving 953 mg (99%) Compound VI-3.

Compound VI-3:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.86 (s, 2 H), 6.66 (s, 2 H), 4.68 (s, 2 H), 3.66 (s, 3 H), 1.80 (br s, 1 H), 1.37 (s, 18 H)

[ 0055 ]

950 mg (1.60 mmol) Compound VI-3 was dissolved in 6 mL methanol-free methylene chloride, 689 mg (3.20 mmol) PCC was added, and the ingredients were stirred for 1 hour at room temperature. The reaction solution was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:4), giving 748 mg (79%) Compound VI-4.

Compound VI-4:

$^1$H-NMR (400 MHz, $CDCl_3$) 9.88 (s, 1 H), 8.35 (s, 2 H), 6.65 (s, 2 H), 3.67 (s, 3 H), 1.37 (s, 18 H)

[ 0056 ]

717 mg (3.78 mmol) $TiCl_4$ dissolved in 3 mL carbon tetrachloride was added over a period of 15 minutes to 10 mL THF cooled on ice in an argon atmosphere. When yellow precipitate was produced, a 15 mL THF solution of 745 mg (1.26 mmol) Compound VI-4, 177 mg (1.51 mmol) thiazolidinedione, and 1.3 mL (16.6 mmol) anhydrous pyridine was added at 0°C, and the ingredients were stirred for 4 hours at room temperature. The reaction solution was extracted with ethyl acetate, the solids were filtered off, and the filtrate was washed with water, 2 N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and aqueous sodium chloride, in that order, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1), giving 597 mg (69%) Compound 7.

Compound 7: colorless rod-shaped crystals (ethyl acetate/n-hexane); m.p. 245°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.69 (b, 1 H), 8.13 (s, 2 H), 7.75 (s,1 H), 6.62 (s, 2 H), 3.63 (s, 3 H),1.37 (s, 18 H);

Anal. Calcd for $C_{23}H_{27}NO_4Si_2$ C: 43.43 %, H: 3.94 %, N: 2.03 %, Found C:43.33 %, H: 3.82 %, N: 1.82 %

[ 0057 ] Example 8: Synthesis of Compound 8

3.67 g (7.18 mmol) Compound VII-1 was suspended in 30 mL anhydrous methylene chloride, and 500 mg copper powder was added. 2.00 g (4.78 mmol) Compound I-1 and 0.6 mL triethylamine were added while cooled on ice, and the mixture was stirred for 20 hours at room temperature. The reaction solution was filtered, and the filtrate was extracted with methylene chloride. The organic phase was washed with 2 N hydrochloric acid and aqueous sodium chloride, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:10), giving 1.78 g (66%) Compound VII-2.

Compound VII-2:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.50 (s, 2 H), 6.78 (d, J = 8.8 Hz, 1 H), 6.70 (d, J = 8.8 Hz, 1 H), 6.40 (dd, J = 8.8, 3.1 Hz, 1 H), 4.39 (q, J = 6.9 Hz, 2 H), 3.79 (s, 3 H), 3.29 (h, J = 7.1 Hz, 1 H), 1.41 (t, J = 7.0 Hz,3 H), 1.17 (d, J = 6.8 Hz, 6 H)

[ 0058 ]

1.78 g (3.14 mmol) Compound VII-2 was dissolved in 10 mL THF, 9.43 mL (9.43 mmol) DIBAL (1 M toluene solution) was gradually added at 0°C, and the ingredients were stirred for 30 minutes. The reaction solution was poured into 2 N hydrochloric acid and extracted with ether. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, giving 1.65 g (quantitative) crude product of Compound VII-3.

Compound VII-3:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.85 (s, 2 H), 6.80 (d, J = 3.1 Hz, 1 H), 6.69 (d, J = 9.0 Hz, 1 H), 6.40 (dd, J = 9.0, 3.1 Hz, 1 H), 4.66 (d, J = 5.9 Hz, 2 H), 3.78 (s, 3 H), 3.28 (h, J = 7.0 Hz, 1 H), 1.78 (t, J = 6.0 Hz,1 H), 1.18 (d, J = 7.0 Hz, 6 H)

[ 0059 ]

1.65 g (3.15 mmol) Compound VII-3 was dissolved in 8 mL methanol-free methylene chloride, 1.37 g (6.34 mmol) PCC was added, and the ingredients were stirred for 1.5 hours at room temperature. The reaction solution was purified by silica gel column chromatography, giving 1.46 g (85%) Compound VII-4.

Compound VII-4:

$^1$H-NMR (400 MHz, $CDCl_3$) 9.88 (s, 1 H), 8.35 (s, 2 H), 6.79 (d, J = 3.1 Hz, 1 H), 6.71 (d, J = 9.0 Hz, 1 H), 6.40 (dd, J = 8.9, 3.1 Hz, 1 H), 3.79 (s, 3 H), 3.29 (h, J = 7.0 Hz, 1 H), 1.18 (d, J = 7.0 Hz, 6 H)

[ 0060 ]

1.54 g (8.05 mmol) $TiCl_4$ dissolved in 8 mL carbon tetrachloride was added over a period of 15 minutes to 20 mL THF cooled on ice in an argon atmosphere. When yellow precipitate was produced, a 5 mL THF solution of 1.40 g (2.68 mmol) Compound VII-4, 376 mg (3.22 mmol) thiazolidinedione, and 2.8 mL (35 mmol) anhydrous pyridine was added at 0°C, and the ingredients were stirred for 16 hours at room temperature. The reaction solution was extracted with ethyl acetate, the solids were filtered off, and the filtrate was washed with water, 2 N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and aqueous sodium chloride, in that order, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1), giving 1.41 g (84%) Compound VII-5.

Compound VII-5:

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.70 (b, 1 H), 8.
11 (s, 2 H), 7.74 (s,1 H), 6.84 (d, J = 8.8 Hz, 1
H), 6.74 (d, J = 2.9 Hz, 1 H), 6.35 (dd, J= 8.8,
2.9 Hz, 1 H), 4.02 (h, J = 7.1 Hz, 1 H), 3.28 (s,
3 H), 1.12 (d,J = 6.9 Hz, 6 H)

[ 0061 ]

1.45 g (2.25 mmol) Compound VII-5 was suspended in 8 mL anhydrous methylene chloride, 4.51 mL (4.51 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 6 hours. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic layer was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1), giving 842 mg (62%) Compound 8.

Compound 8: colorless powder (THF/ethyl acetate/n-hexane); m.p. 222°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.69 (b, 1 H), 9.
00 (s, 1 H), 8.10 (s,2 H), 7.73 (s, 1 H), 6.66 (d,
J = 8.8 Hz, 1 H), 6.64 (d, J = 2.9 Hz, 1 H), 6.23

(dd, J = 8.8, 2.9 Hz, 1 H), 3.15 (h, J = 6.8 Hz, 1 H), 1.11 (d,J = 6.8 Hz, 6 H);
Anal. Calcd for $C_{19}H_{15}NO_4SI_2$ C: 37.58 %, H: 2.49 %, N: 2.31 %, Found C:37.43 %, H: 2.52 %, N: 2.13 %

[ 0062 ] Example 9: Synthesis of Compound 9

2.66 g (5.20 mmol) Compound VII-1 was suspended in 17 mL anhydrous methylene chloride, and 413 mg copper powder was added. 488 mg (6.00 mmol) p-hydroxybenzaldehyde and 0.5 mL triethylamine were added while cooled on ice, and the ingredients were stirred for 6 hours at room temperature. The reaction solution was filtered and extracted with methylene chloride. The organic phase was washed with 2 N hydrochloric acid and aqueous sodium chloride, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:8), giving 796 mg (74%) Compound VIII-1.

Compound VIII-1:

$^1$H-NMR (400 MHz, $CDCl_3$) 9.90 (s, 1 H), 7.81 (d. J = 8.4 Hz, 2 H), 7.00 (d, J = 8.6 Hz, 2 H), 6.95 (d, J = 2.6 Hz, 1 H), 6.83-6.89 (m, 2 H), 3.85(s, 3 H), 3.32 (h, J = 7.0 Hz, 1 H), 1.19 (d, J = 7.0 Hz, 6 H)

[ 0063 ]

1.67 g (8.78 mmol) $TiCl_4$ dissolved in 8 mL carbon tetrachloride was added over a period of 15 minutes to 20 mL THF cooled on ice in an argon atmosphere. When yellow precipitate was produced, a 20 mL THF solution of 790 mg (2.93 mmol) Compound VIII-1, 411 mg (3.52 mmol) thiazolidinedione, and 3 mL (39 mmol) anhydrous pyridine was added at 0°C, and the ingredients were stirred for 6 hours at room temperature. The reaction solution was extracted with ethyl acetate, the solids were filtered off, and the filtrate was washed with water, 2 N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and aqueous sodium chloride, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:2), giving 831 mg (77%) Compound VIII-2.

Compound VIII-2:

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.51 (br s, 1 H), 7.74 (s, 1 H), 7.58 (d, J = 9.1 Hz, 2 H), 7.01 (d, J = 9.1 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 1 H), 6.96 (d, J = 2.9 Hz, 1 H), 6.91 (dd, J = 8.8, 2.9 Hz, 1 H), 3.80 (s,3 H), 1.13 (s, 6 H)

[ 0064 ]

100 mg (0.27 mmol) Compound VIII-2 was suspended in 2 mL anhydrous methylene chloride, 0.81 mL (0.81 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 3 hours. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic layer was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:3 → ethyl acetate), giving 89.5 mg (93%) Compound 9.

Compound 9: yellow plate-shaped crystals (ethyl acetate); m.p. 206°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.50 (br s, 1 H), 9.32 (s, 1 H), 7.73 (s, 1 H), 7.56 (d, J = 8.8 H

z, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 6.87 (d,J = 2. 7 Hz, 1 H), 6.82 (d, J = 8.6 Hz, 1 H), 6.75 (dd, J = 8.5, 2.9 Hz,1 H), 3.21 (h, J = 7.0 Hz, 1 H), 1. 13 (d, J = 6.8 Hz, 6 H)

[ 0065 ] Example 10: Synthesis of Compound 10

2.66 g (5.20 mmol) Compound VII-1 was suspended in 17 mL anhydrous methylene chloride, and 413 mg copper powder was added. 600 mg (4.00 mmol) 3,5-dimethyl-4-hydroxybenzaldehyde and 0.5 mL triethylamine were added while cooled on ice, and the ingredients were stirred for 7 hours at room temperature. The reaction solution was filtered, and the filtrate was extracted with methylene chloride. The organic phase was washed with 2 N hydrochloric acid and aqueous sodium chloride, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:10), giving 886 mg (74%) Compound VIII-1.

Compound VIII-1:

$^1$H-NMR (400 MHz, $CDCl_3$) 9.94 (s, 1 H), 7.63 (s, 2 H), 6.75 (d, J = 3.1 Hz, 1 H), 6.67 (d, J = 8.8 Hz, 1 H), 6.35 (dd, J = 8.8, 3.1 Hz, 1 H), 3.77 (s, 3 H), 3.27 (h, J = 7.0 Hz, 1 H), 2.197 (s, 3 H), 2.195 (s, 3 H), 1.16 (d, J = 7.0 Hz, 6 H)

[ 0066 ]

1.69 g (8.86 mmol) $TiCl_4$ dissolved in 8 mL carbon tetrachloride was added over a period of 15 minutes to 22 mL THF cooled on ice in an argon atmosphere. When yellow precipitate was produced, a 22 mL THF solution of 880 mg (2.95 mmol) Compound VIII-1, 415 mg (3.54 mmol) thiazolidinedione, and 3.1 mL (39 mmol) anhydrous pyridine was added at 0°C, and the ingredients were stirred for 4.5 hours at room temperature. The reaction solution was extracted with ethyl acetate, the solids were filtered off, and the filtrate was washed with water, 2 N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and aqueous sodium chloride, in that order, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:2), giving 934 mg (80%) Compound VIII-2.

Compound VIII-2:

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.56 (br s, 1 H), 7.71 (s, 2 H), 7.38 (s, 2 H), 6.81 (d, J = 9.0 Hz, 1 H), 6.75 (d, J = 3.1 Hz, 1 H), 6.34 (dd, J = 9.0, 3.1 Hz, 1 H), 3.72 (s, 3 H), 3.19 (h, J = 6.8 Hz, 1 H), 2.10 (s, 6 H), 1.10 (d, J = 6.8 Hz, 6 H)

[ 0067 ]

100 mg (0.25 mmol) Compound VIII-2 was suspended in 2 mL anhydrous methylene chloride, 0.76 mL (0.76 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 2 hours. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic layer was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the

residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:2), giving 96 mg (99%) Compound 10.

Compound 10: colorless plate-shaped crystals (ethyl acetate); m.p. 210°C

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.56 (br s, 1 H), 8.92 (s, 1 H), 7.70 (s, 1 H), 7.37 (s, 2 H), 6.64 (d, J = 8.6 Hz, 1 H), 6.63 (d, J = 3.0 Hz,1 H), 6.23 (dd, J = 8.6, 3.0 Hz, 1 H), 3.16 (h, J = 7.0 Hz, 1 H), 2.09 (s, 6 H), 1.09 (d, J = 7.1 Hz, 6 H)

[ 0068 ] Example 11: Synthesis of Compound 11

3.94 g (9.20 mmol) Compound I-2 was suspended in 30 mL anhydrous methylene chloride, and 793 mg copper powder was added. 3.00 g (7.67 mmol) Compound IX-1 and 1 mL triethylamine were added while cooled on ice, and the mixture was then stirred for 20 hours at room temperature. The reaction solution was filtered, and the filtrate was extracted with methylene chloride. The organic phase was washed with 2 N hydrochloric acid and aqueous sodium chloride, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:2), giving 1.10 g (40%) Compound IX-2.

Compound IX-2:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.72 (s, 2 H), 6.85 (d, J = 9.2 Hz, 2 H), 6.71 (d, J = 9.0 Hz, 2 H), 3.79 (s, 3 H)

[ 0069 ]

1.09 g (2.24 mmol) Compound IX-2 was dissolved in 18 mL ethyl acetate, 300 mg Pt-C was added, and catalytic hydrogen reduction was brought about at room temperature. After 1 hour, 200 mg of 5% Pt-C and 3 mL ethyl acetate were added. After 2 hours, the solution was filtered with celite, the solvent was distilled off, and the residue was purified by silica gel column chromatography (methylene chloride:n-hexane = 1:2), giving 748 mg (73%) Compound IX-3.

Compound IX-3:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.14 (s, 2 H), 6.80 (d, J = 9.2 Hz, 2 H), 6.70 (d, J = 9.2 Hz, 2 H), 3.75 (s, 3 H), 3.62 (br s, 2 H)

[ 0070 ]

1.47 g (3.32 mol) Compound IX-3 was dissolved in 16 mL acetone and 4 mL water, 1.1 mL concentrated hydrochloric acid was added, and the mixture was allowed to stand at -15°C. 346 mg (5.02 mmol) sodium sulfite was dissolved in 6.5 mL water and gradually added, and the ingredients were stirred for 15 minutes. 4.12 mL (38.6 mmol) ethyl acrylate was added in the form of drops, and 164 mg (1.16 mmol) copper chloride (I) was gradually added at 40°C. After 20 minutes, the reaction solution was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:10) and then flash silica gel column chromatography (ethyl acetate:n-hexane = 1:20), giving 318 mg (18%) Compound IX-4.

Compound IX-4:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.72 (s,2 H), 6.82 (d, J = 9.3 Hz, 2 H), 6.69 (d, J = 9.2 Hz, 2 H), 4.41 (dd, J = 7.7, 6.8 Hz, 1 H), 4.24 (q, J = 7.2 Hz, 2 H), 3.77 (s, 3 H), 3.29 (dd, J = 14.3, 6.8 Hz, 1 H), 3.11 (dd, J = 14.1, 7.7 Hz, 1 H), 1.29 (t, J = 7.2 Hz, 3 H)

[ 0071 ]

314 mg (0.56 mmol) Compound IX-4 and 54 mg (0.71 mmol) thiourea were dissolved in 10 mL sulfolan, and the mixture was stirred for 90 minutes at 120°C. A mixture of 14 mL acetic acid, 3 mL concentrated hydrochloric acid, and 1.5 mL water was added to the reaction solution at room temperature, and the ingredients were then stirred for 18 hours at 90°C. Sodium bicarbonate was added to the reaction solution, and after the carbon dioxide had finished coming out, the solution was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate aqueous solution and aqueous sodium chloride, and was then dried over $MgSO_4$. The

solvent was distilled off, and the residue was purified by flash silica gel column chromatography (ethyl acetate:n-hexane = 1:4 → 1:3), giving 53 mg (17%) Compound IX-5.

Compound IX-5:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.73 (s, 2 H), 6.83 (d, J = 9.0 Hz, 2 H), 6.69 (d, J = 9.1 Hz, 2 H), 4.53 (dd, J = 9.5, 4.0 Hz, 1 H), 3.78 (s, 3 H), 3.47 (dd, J = 14.3, 4.0 Hz, 1 H), 3.10 (dd, J = 14.1, 9.4 Hz, 1 H)

[ 0072 ]

53 mg (0.094 mmol) Compound IX-5 was dissolved in 2 mL anhydrous methylene chloride, 0.28 mL (0.28 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 3 hours. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic layer was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, giving 46 mg (90%) crude product of Compound IX-6.

Compound IX-6:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.06 (br s, 1 H), 7.73 (s, 2 H), 6.77 (d, J = 9.0 Hz, 2 H), 6.64 (d, J = 9.0 Hz, 2 H), 4.70 (s, 1 H), 4.52 (dd, J = 9.5,4.0 Hz, 1 H), 3.46 (dd, J = 14.3, 4.0 Hz, 1 H), 3.09 (dd, J = 14.3, 9.5Hz, 1 H)

[ 0073 ]

45 mg (0.082 mmol) Compound IX-5 was dissolved in 2 mL aqueous ammonia, 84 mg (0.51 mmol) potassium iodide and 25 mg (0.098 mmol) iodine were dissolved in 1 mL water and added, and the ingredients were stirred for 40 minutes at room temperature. 2 N hydrochloric acid was added to the reaction solution to render it acidic, and it was extracted with ethyl acetate. The organic phase was washed with sodium bisulfite aqueous solution and aqueous sodium chloride, and it was dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by flash silica gel column chromatography (twice, with methylene chloride:ethyl acetate = 4:1 and 10:1), giving 26 mg (48%) Compound 11.

Compound 11: colorless oil

$^1$H-NMR (400 MHz, $CDCl_3$) 8.10 (br s, 1 H), 7.73 (s, 2 H), 7.07 (d, J = 2.9 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 6.65 (dd, J = 9.0, 2.9 Hz, 1 H),5.07 (s, 1 H), 4.53 (dd, J = 9.5, 4.1 Hz, 1 H), 3.47 (dd, J = 14.1, 4.0Hz, 1 H), 3.10 (dd, J = 14.3, 9.5 Hz, 1 H)

[ 0074 ] Example 12: Synthesis of Compound 12

3.32 g (6.14 mmol) Compound IV-1 was suspended in 30 mL anhydrous methylene chloride, and 529 mg (8.33 mmol) copper powder was added. 2.00 g (5.11 mmol) Compound IX-1 and 0.7 mL (5.11 mmol) triethylamine were added while cooled on ice, and the ingredients were then stirred for 40 hours at room temperature. The organic phase was washed with 2 N hydrochloric acid and aqueous sodium chloride, and was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:20), giving 1.47 g (52%) Compound IX-7.

Compound IX-7:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.37 (s, 2 H), 6.88 (d, J = 8.8 Hz, 1 H), 6.81 (d, J = 3.1 Hz, 1 H), 6.40 (dd, J = 8.8, 3.1 Hz, 1 H), 3.28 (s, 3 H), 1.30 (s, 9 H)

[ 0075 ]

920 mg (1.66 mmol) Compound IX-7 was dissolved in 25 mL ethyl acetate and 5 mL ethanol, 200 mg of 5% Pt-C was added, and catalytic hydrogen reduction was brought about at room temperature. After 5 hours, 100 mg of Pt-C was added, and the mixture was stirred for another 8 hours. The reaction solution was filtered with celite, the solvent was distilled off, and the residue was purified by silica gel column chromatography (chloroform), giving 648 mg (75%) Compound IX-8.

Compound IX-8:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.16 (s, 2 H), 6.90 (d, J = 3.1 Hz, 1 H), 6.71 (d, J = 8.8 Hz, 1 H), 6.42 (dd, J = 8.8, 3.1 Hz, 1 H), 3.78 (s, 3 H), 3.62 (br s, 2 H), 1.35 (s, 9 H)

[ 0076 ]

220 mg (0.42 mmol) Compound IX-8 was dissolved in 3 mL acetone and 0.7 mL water, 0.15 mL concentrated hydrochloric acid was added, and the mixture was allowed to stand at -15°C. 38 mg (0.55 mmol) sodium bisulfite was dissolved in 1 mL water and gradually added, and the ingredients were stirred for 15 minutes. 0.46 mL (4.20 mmol) ethyl acrylate was added in the form of drops, and 18 mg (0.13 mmol) copper oxide was gradually added at 40°C. After 20 minutes, the reaction solution was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:10), giving 81 mg (30%) Compound IX-9.

Compound IX-9:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.72 (s, 2 H), 6.89 (d, J = 3.1 Hz, 1 H), 6.70 (d, J = 8.9 Hz, 1 H), 6.36 (dd, J = 8.8, 3.1 Hz, 1 H), 4.41 (t, J = 7.0 Hz, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 3.79 (s, 3 H), 3.29 (dd, J = 14.0, 7.0 Hz, 1 H), 3.10 (dd, J = 14.0, 7.5 Hz, 1 H), 1.34 (s, 9 H), 1.29 (t, J= 7.1 Hz, 3 H)

[ 0077 ]

147 mg (0.23 mmol) Compound IX-9 and 22 mg (0.29 mmol) thiourea were dissolved in 3 mL sulfolan, and the ingredients were stirred for 90 minutes at 120°C. A mixture of 6 mL acetic acid, 2 mL concentrated hydrochloric acid, and 1 mL water were added to the reaction solution at room temperature, and the mixture was stirred for 20 hours at 90°C. Sodium bicarbonate was added to the reaction solution, and when the carbon dioxide had finished coming out, the solution was extracted with ethyl acetate. The organic phase was washed with saturated sodium

bicarbonate aqueous solution and aqueous sodium chloride, and it was dried over $MgSO_4$. The solvent was distilled off, giving 33 mg (22%) crude product of Compound IX-10.

Compound IX-10:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.16 (br, 1 H), 7.73 (s, 2 H), 6.88 (d, J = 3.1Hz, 1 H), 6.71 (d, J = 9.0 Hz, 1 H), 6.37 (dd, J = 8.8, 3.1 Hz, 1 H), 4.53 (dd, J = 9.5, 4.2 Hz, 1 H), 3.79 (s, 3 H), 3.46 (dd, J = 14.1, 4.0 Hz, 1 H), 3.09 (dd, J = 14.3, 9.5 Hz, 1 H), 1.34 (s, 9 H)

[ 0078 ]

45 mg (0.070 mmol) Compound IX-10 was suspended in 2 mL anhydrous methylene chloride, 0.21 mL (0.21 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 1 hour. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1) and flash silica gel column chromatography (methylene chloride:ethyl acetate = 100:1), giving 32 mg (75%) Compound 12.

Compound 12: colorless oil

$^1$H-NMR (400 MHz, $CDCl_3$) 7.97 (b, 1 H), 7.73 (s, 2 H), 6.86 (d, J = 2.9 Hz, 1 H), 6.86 (d, J = 2.9 Hz, 1 H), 6.54 (d, J = 8.6 Hz, 1 H), 6.30 (dd, J = 8.5, 3.2 Hz, 1 H), 4.58 (s, 1 H), 4.53 (dd, J = 9.3, 4.2 Hz, 1 H), 3.46 (dd, J = 14.2, 4.1 Hz, 1 H), 3.10 (dd, J = 14.4, 9.5 Hz, 1 H), 1.38(s, 9 H)

[ 0079 ] Example 13: Synthesis of Compound 13

4.40 g (8.59 mmol) Compound VII-1 was suspended in 30 mL anhydrous methylene chloride, and 740 mg copper powder was added. 2.80 (7.16 mmol) Compound IX-1 and 0.9 mL triethylamine were added while cooled on ice, and the ingredients were stirred for 24 hours at room temperature. The reaction solution was filtered, and the filtrate was extracted with methylene chloride. The organic phase was washed with 2 N hydrochloric acid and aqueous

sodium chloride, and it was dried over $MgSO_4$. The solvent was distilled off, and the residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:10), giving 3.50 g (91%) Compound IX-11.

Compound IX-11:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.73 (s, 2 H), 6.79 (d, J = 3.1 Hz, 1 H), 6.71 (d, J = 9.0 Hz, 1 H), 6.39 (dd, J = 8.8, 3.1 Hz, 1 H), 3.80 (s, 3 H), 3.29 (h, J = 6.8 Hz, 1 H), 1.18 (d, J = 7.0 Hz, 6 H).

[ 0080 ]

3.50 g (6.49 mmol) Compound IX-11 was dissolved in 30 mL ethyl acetate, 1.0 g of 5% Pt-C was added, and catalytic hydrogen reduction was brought about at room temperature. After 4 hours, the solution was filtered with celite, the solvent was distilled off, and the residue was then purified by silica gel column chromatography (chloroform), giving 3.35 g (quantitative) Compound IX-12.

Compound IX-12:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.16 (s, 2 H), 6.78 (d, J = 2.9 Hz, 1 H), 6.69 (d, J = 8.8 Hz, 1 H), 6.43 (dd, J = 8.8, 3.1 Hz, 1 H), 3.78 (s, 3 H), 3.63 (s, 2 H), 3.28 (h, J = 7.0 Hz, 1 H), 1.18 (d, J = 7.0 Hz, 6 H)

[ 0081 ]

3.30 g (6.48 mmol) Compound IX-12 was dissolved in 32 mL acetone and 8 mL water, 2.1 mL concentrated hydrochloric acid was added, and the mixture was allowed to stand at -15°C. 582 mg (8.43 mmol) sodium bisulfite was dissolved in 12 mL water and then gradually added, and the mixture was stirred for 15 minutes. 7.01 mL (64.8 mmol) ethyl acrylate was added in the form of drops, and 276 mg (1.94 mmol) copper oxide was then gradually added at 40°C. After 30 minutes, the reaction solution was extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by flash silica gel column chromatography (ethyl acetate:n-hexane = 1:20), giving 788 mg (19%) Compound IX-13.

Compound IX-13:

$^1$H-NMR (400 MHz, $CDCl_3$) 7.72 (s, 2 H), 6.78 (d, J = 2.9 Hz, 1 H), 6.69 (d, J = 8.8 Hz, 1 H), 6.37 (d d, J = 9.0, 3.0 Hz, 1 H), 4.42 (t, J = 7.5 Hz, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 3.78 (s, 3 H), 3.28 (m, 2 H), 3.11 (dd, J = 13.0, 7.5 Hz, 1 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.18 (d, J = 7.0Hz, 6 H)

[ 0082 ]

783 mg (1.25 mmol) Compound IX-13 and 121 mg (1.58 mmol) thiourea were dissolved in 6 mL sulfolan, and the mixture was stirred for 90 minutes at 120°C. A mixture of 9 mL acetic acid, 6.7 mL concentrated hydrochloric acid, and 3.3 mL water was added to the reaction solution at room temperature, and the ingredients were stirred for 17 hours at 90°C. Sodium bicarbonate was added to the reaction solution, and when the carbon dioxide had finished coming out, the solution was extracted with ether. The organic phase was washed with saturated sodium bicarbonate aqueous solution and aqueous sodium chloride, and it was dried over $MgSO_4$. The solvent was distilled off, and the residue was then purified by flash silica gel column chromatography (ethyl acetate:n-hexane = 1:3), giving 318 mg (40%) Compound IX-14.

Compound IX-14:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.07 (br s, 1 H), 7.73 (s, 2 H), 6.78 (d, J = 3.1 Hz, 1 H), 6.70 (d, J = 8.8 Hz, 1 H), 6.36 (dd, J = 9.0, 3.1 Hz, 1 H),4.53 (d d, J = 9.5, 4.2 Hz, 1 H), 3.78 (s, 3 H), 3.47 (dd, J = 14.3, 4.2Hz, 1 H), 3.28 (h, J = 7.0 hz, 1 H), 3.10 (dd, J = 14.1, 9.6 Hz, 1 H), 1.18 (d, J = 6.8 Hz, 6 H)

[ 0083 ]

312 mg (0.49 mmol) Compound IX-14 was suspended in 5 mL anhydrous methylene chloride, 1.48 mL (1.48 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 1.2 hours. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the

residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 4:5), giving 302 mg (99%) Compound 13.

Compound 13: colorless oil

$^1$H-NMR (400 MHz, $CDCl_3$) 8.03 (br s, 1 H), 7.73 (s, 2 H), 6.75 (d, J = 3.1 Hz, 1 H), 6.63 (d, J = 8.6 Hz, 1 H), 6.31 (dd, J = 8.6, 3.1 Hz, 1 H),4.53 (d d, J = 9.3, 4.0 Hz, 1 H), 4.51 (s, 1 H), 3.47 (dd, J = 14.3, 4.0Hz, 1 H), 3.17 (h, J = 7.0 Hz, 1 H), 3.10 (dd, J = 9.5 Hz, 1 H), 1.22 (d, J = 6.8 Hz, 6 H)

[ 0084 ] Example 14: Synthesis of Compound 14

703 mg (1.91 mmol) Compound VIII-2 was dissolved in 10 mL DMF, 500 mg of 10% Pd-C was added, and catalytic hydrogen reduction was brought about at 50°C. After 1 hour, 500 mg of 10% Pd-C and 2 mL DMF were added. After another 2 hours, 500 mg of 10% Pd-C and 4 mL of DMF were added. After 6 hours, the reaction solution was filtered with celite and concentrated. The residue was purified by flash silica gel column chromatography (ethyl acetate:n-hexane = 1:4, twice), giving 440 mg (62%, starting material recovered 77 mg) Compound VIII-3.

Compound VIII-3:

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 11.99 (br s, 1 H), 7.19 (d, J = 8.5 Hz,2 H), 6.94 (d, J = 8.8 Hz, 1 H), 6.88 (d, J = 2.9 Hz, 1 H), 6.84 (d, J =8.5 Hz, 2 H), 6.79 (dd, J = 8.8, 2.9 Hz, 1 H), 4.86 (dd, J = 9.3, 4.4 Hz, 1 H), 3.77 (s, 3 H), 3.33 (dd, J = 13.9, 4.4 Hz, 1 H), 3.22 (h, J = 7.0 Hz, 1 H), 3.07 (dd, J = 14.1, 9.0 Hz, 1 H) 1.11 (d, J = 7.0 Hz, 6 H)

[ 0085 ]

340 mg (0.92 mmol) Compound VIII-3 was suspended in 6 mL anhydrous methylene chloride, 2.75 mL (2.75 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 3 hours. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and extracted with methylene chloride. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and

the residue was then purified by flash silica gel column chromatography (ethyl acetate:n-hexane = 1:2), giving 328 mg (quantitative) Compound 14.

Compound 14: colorless oil

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 11.99 (br s, 1 H), 9.18 (s, 1 H), 7.17 (d, J = 8.8 Hz, 2 H), 6.81 (d, J = 8.6 Hz, 2 H), 6.79 (d, J = 2.9 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H), 6.65 (dd, J = 8.8, 2.9 Hz, 1 H), 4.85 (dd, J = 9.3, 4.4 Hz, 1 H), 3.32 (dd, J = 14.1, 4.4 Hz, 1 H), 3.19 (h, J = 6.8 Hz, 1 H), 3.06 (dd, J = 14.3, 9.5 Hz, 1 H), 1.11 (d, J = 7.1 Hz, 6 H)

[ 0086 ] Example 15: Synthesis of Compound 15

828 mg (20.9 mmol) Compound VIII-5 was dissolved in 15 mL DMF, 600 mg of 10% Pd-C was added, and catalytic hydrogen reduction was brought about at 50°C. After 2 hours, 300 mg of 10% Pd-C and 2 mL DMF were added. After 5 hours, the reaction solution was filtered with celite, the solvent was distilled off, and the residue was purified by flash silica gel column chromatography (ethyl acetate:n-hexane = 1:4), giving 674 mg (81%, starting material recovered 144 mg) Compound VIII-6.

Compound VIII-6:

$^1$H-NMR (400 MHz, $CDCl_3$) 8.15 (br s, 1 H), 6.94 (s, 2 H), 6.75 (d, J = 11.4, 3.1 Hz, 1 H), 6.66 (d, J = 13.9, 2.8 Hz, 1 H), 6.31 (dd, J = 8.8, 2.9 Hz, 1 H), 4.54 (dd, J = 10.1, 2.8 Hz, 1 H), 3.76 (s, 3 H), 3.52 (dd, J= 13.9, 2.8 Hz, 1 H), 3.05 (dd, J = 14.1, 10.3 Hz, 1 H), 2.11 (s, 6 H),1.16 (d, J = 6.8 Hz, 6 H)

[ 0087 ]

670 mg (1.68 mmol) Compound VIII-6 was suspended in 5 mL anhydrous methylene chloride, 5.04 mL (5.04 mmol) $BBr_3$ (1 M methylene chloride solution) was added at 0°C, and the ingredients were stirred for 2.5 hours. The reaction solution was poured into saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic phase was washed with aqueous sodium chloride and dried over $MgSO_4$. The solvent was distilled off, and the

residue was then purified by silica gel column chromatography (ethyl acetate:n-hexane = 2:3), giving 542 mg (84%) Compound 15.

Compound 10 [sic]: colorless oil

$^1$H-NMR (400 MHz, DMSO-$d_6$, 30°C) 12.02 (br s, 1 H), 8.84 (s, 1 H), 7.00 (s, 2 H), 6.62 (d, J = 8.5 Hz, 1 H), 6.55 (d, J = 3.1 Hz, 1 H), 6.19 (dd, J = 12.9, 8.5 Hz, 1 H), 4.89 (dd, J = 9.5, 3.4 Hz, 1 H), 3.34 (dd, J =14.2, 4.4 Hz, 1 H), 3.13 (h, J = 6.8 Hz, 1 H), 3.03 (dd ,J = 13.9, 9.5 Hz, 1 H), 2.01 (s, 6 H), 1.07 (d, J = 6.8 Hz, 6 H)

[ 0088 ] Test Example 1: Test of activation of thyroid hormone receptor transcription in COS-1 cells

COS-1 cells incorporating a human thyroid hormone nuclear receptor α (hTRα) expression vector and a reporter plasmid (TREpalx3-TKLUC) were used to assay ligand-dependent transcription activation with a luciferase system by Promega. The results in Tables 2 and 3 are relative values, where 1 is the transcription activation when only solvent was added as a negative control. The concentrations are given in terms of logarithmic values.

[ 0089 ]

[ Table 2 ]

| Com-pounds | Concentrations | | | |
|---|---|---|---|---|
| | -9 | -8 | -7 | -6 |
| T3 | 11.7 | 30.5 | 38.6 | |
| 1 | 1.8 | 1.7 | 5.5 | 30.5 |
| 5 | 1.5 | 2.2 | 5.5 | 28.7 |
| 11 | 2.6 | 6.9 | 29.9 | 37.8 |
| 12 | 3.5 | 16.3 | 32.4 | 32.5 |

[ 0090 ]

[ Table 3 ]

| Com-pounds | Concentrations | | | |
|---|---|---|---|---|
| | -9 | -8 | -7 | -6 |
| T3 | 4.9 | 20.0 | 24.6 | |
| 2 | 1.1 | 1.0 | 1.3 | 3.7 |
| 3 | 1.5 | 1.2 | 1.2 | 1.6 |
| 4 | 1.3 | 1.0 | 1.6 | 6.8 |
| 6 | 1.0 | 1.2 | 1.0 | 0.9 |
| 7 | 1.3 | 1.5 | 1.4 | 1.3 |
| 8 | 1.3 | 1.9 | 8.0 | 27.9 |
| 13 | 3.4 | 18.3 | 26.4 | 28.7 |

[ 0091 ]

[ Effects of the Invention ]

The compounds of the invention have thyroid hormone-like action, and are useful as active ingredients in medicinal compositions for the treatment and/or prevention of diseases such as obesity, hypercholesterolemia, and atherosclerosis.